REMARKS

Claims 1-12 and 21-23 are pending in the present application. With the instant amendments, claims 1 and 8 are amended, and claim 23 is canceled without prejudice. Upon entry of these amendments, claims 1-12 and 21-22 will be pending and under consideration. Applicants reserve the right to prosecute the subject matter of any canceled claim in one or more continuation or divisional or continuation-in-part applications.

I. AMENDMENTS TO THE CLAIMS

Claim 1 has been amended to recite as follows: "[a] method for ameliorating a symptom of ethanol intolerance in a subject with reduced or absent aldehyde dehydrogenase subtype 2 (ALDH2) activity comprising ...".

Claim 8 has been amended to recite as follows: "[a] method of reducing a symptom associated with acetaldehyde accumulation accompanying ethanol consumption in a subject with reduced or absent aldehyde dehydrogenase subtype 2 (ALDH2) activity comprising ...".

Applicants submit that the amendments to the claims are fully supported by the specification as originally filed and present no new matter. Entry thereof is respectfully requested.

II. CLAIM REJECTIONS UNDER 35 U.S.C. § 112, first paragraph

Claims 1-12 and 21-23 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The rejection of claim 23 is moot since this claim has been canceled.

The Patent Office acknowledges that the specification is enabling for methods of ameliorating a symptom of ethanol intolerance in a subject with reduced or absent ALDH2 activity. The Patent Office alleges that the specification does not reasonably provide enablement for methods of *preventing*. Without acquiescing to the propriety of the rejection, and solely to expedite prosecution of the claims, Applicants amended independent claims 1 and 8, which as amended, do not recite "preventing." Applicants respectfully submit that independent claims 1 and 8, as well as claims 2-7, 9, 11, 21 and 22 that depend directly or indirectly from claim 1 and/or claim 8, are fully enabled by the specification as filed.

Claims 10 and 12 recite methods of ameliorating a symptom of acetaldehyde accumulation accompanying ethanol consumption. These two claims do not recite methods for *preventing* a symptom of ethanol intolerance.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-12 and 21-23 for lack of enablement under 35 U.S.C. § 112, first paragraph.

III. CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

Claim 1-12 and 21-23 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Japanese Unexamined Patent Application S57-106620(5) ("the '620 application") in view of Casavant, *Pediatrics*, Vol. 107, No. 1, January 2001, pp. 170 ("Casavant"), and Jacobsen *et al.*, 1996, *Alcoholism: Clinical and Experimental Research*, Vol. 20, pp. 804-809 ("Jacobsen *et al.*, 1996").

Applicants respectfully submit that since claim 23 is canceled in the instant amendment, the rejection of this claim under 35 U.S.C. § 103(a) is moot and should be withdrawn.

Applicants respectfully traverse the rejection with respect to claims 1-12, 21 and 22.

A. The legal standard for obviousness

The Supreme Court has addressed the test for obviousness under 35 U.S.C. § 103(a). *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). In *KSR*, the Supreme Court noted that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in a way the claimed new invention does." *KSR*, 127 S.Ct. at 1741. The prior art reference (or references when combined) need not teach or suggest all the claim limitations, however, Office personnel must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art. MPEP § 2141 III at page 2100-118 (Eighth Edition, Rev. 6, September 2007).

Applicants respectfully submit that claims 1-12, 21 and 22 are not obvious over the '620 application in view of Casavant and Jacobsen *et al.*, 1996, because the references, either alone or in combination, do not teach or suggest doses within the range of about 0.1 mg/kg to

about 1.0 mg/kg 4-MP to treat subjects with reduced or absent ALDH2 activity, nor do they provide a reason why one of ordinary skill in the art would use such relatively low doses to treat such subjects.

B. The cited references do not provide a reason why one of ordinary skill in the art would use doses in the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP to treat subjects with reduced or absent ALDH2 activity

The instant claims recite methods comprising administering about 0.1 mg to about 1.0 mg/kg 4-MP to subjects with reduced or absent ALDH2 activity.

The Patent Office acknowledges that the '620 application does not teach or suggest doses within the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP, as recited in the instant claims. *See* Office Action, page 10, paragraph 2.

The '620 application purports to disclose doses of "100 to 500 mg (1.5 to 10 mg/kg) in terms of 4-alkylpyrazole" to alcohol-intolerant adult males. *See* the '620 application, at page 118, first column, fifth paragraph. Further, the '620 application discloses that "[a dose range of 1.5 to 10 mg/kg] in terms of 4-alkylpyrazole is appropriate." *See* the '620 application, at page 118, first column, fifth paragraph. Because the '620 application states that this dose range is appropriate for the intended purpose, one of ordinary skill in the art would have had no reason to lower the dose of 4-MP below 1.5 mg/kg for treating subjects with reduced or absent ALDH2 activity. Neither of the secondary references, Casavant or Jacobsen *et al.*, 1996, provide a reason to lower the dose of 4-MP below 1.5 mg/kg, for example, within the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP to treat subjects with reduced or absent ALDH2 activity.

Casavant describes administration of 4-MP (fomepizole) as a safe and effective blocker of alcohol dehydrogenase. *See* Casavant, at page 170, fourth paragraph. Casavant explains that fomepizole is approved by the Food and Drug Administration to be used as an antidote for treatment of confirmed or suspected ethylene glycol poisoning in adults, and appears equally safe and effective in methanol poisoning in children. *See* Casavant, at page 170, fourth paragraph. In particular, Casavant describes administration of 10 to 15 mg/kg fomepizole as "a 15 mg/kg loading dose ... given intravenously over 30 minutes, followed by 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours ... until

methanol or ethylene glycol levels are < 20 mg/dL." *See* Casavant, at page 170, fourth paragraph. Casavant does not teach, suggest or provide a reason to use doses within the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP to treat subjects with reduced or absent ALDH2 activity, as recited in the instant claims. Indeed, one skilled in the art reading Casavant would have no reason to lower an administered dose of 4-MP below that approved for use as an antidote.

Jacobsen *et al.*, 1996, describes the effect of 4-MP on the rate of ethanol elimination, with the intended purpose of administering 4-MP as an antidote for methanol and/or ethylene glycol poisoning. Jacobsen *et al.*, 1996, purports to disclose that a therapeutic dose range of 10 to 20 mg/kg 4-MP will inhibit alcohol dehydrogenase activity in humans *in vivo* and is effective at blocking methanol or ethylene glycol metabolism. *See* Jacobsen *et al.*, 1996, abstract at page 804, lines 7-12 ("4-MP in the presumed therapeutic dose range of 10 to 20 mg/kg ... inhibit[s] alcohol dehydrogenase activity in humans *in vivo* and would be effective at blocking methanol or ethylene glycol metabolism").

It should be noted that Jacobsen *et al.*, 1996, is a follow-up paper to an earlier Phase I clinical study, described in Jacobsen *et al.*, 1988, *Alcoholism: Clinical and Experimental Research*, Vol. 12, pp. 516-522 ("Jacobsen *et al.*, 1888"). In Jacobsen *et al.*, 1988, an ascending-dose Phase I clinical study was performed to evaluate the safety and pharmacokinetics of 4-MP when administered as an antidote for methanol and/or ethylene glycol poisoning at doses of 10, 20, 50, and 100 mg/kg.[1] The results of the Phase I clinical study led the authors to conclude "a lack of toxicity of 4-MP in terms of all the measured and observed parameters at the doses of 10 and 20 mg/kg." *See* Jacobsen *et al.*, 1988, page 520, column 1, paragraph 2.

According to the Patent Office, Jacobsen *et al.*, 1996, teaches that "lower doses" of 4-MP are effective in treatment but do not have the undesirable side effects of larger doses of 4-MP. *See* Office Action, page 10, paragraphs 2 and 3. According to the Patent Office, it would have been *prima facie* obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have administered 4-MP in the amount 0.1 to 1.0 mg per kg

[1] *See* Jacobsen *et al.*, 1988, abstract at page 516, lines 4-8. The "Phase I clinical study" described in Jacobsen *et al.*, 1988, uses four doses of 4-MP: Group 1 (10 kg/mg), Group 2 (20 kg/mg), Group 3 (50 mg/kg) and Group 4 (100 mg/kg). *See* Jacobsen *et al.*, 1988, page 517, column 1, under "Study Design and Performance."

of body mass to a subject with ethanol intolerance. *See* Office Action, page 10, paragraph 4. Applicants respectfully disagree.

The "lower doses" taught in Jacobsen *et al.*, 1996, are 10 to 20 mg/kg 4-MP.[2] Jacobsen *et al.*, 1996, does not teach or suggest doses below 10 mg/kg 4-MP for oral administration. Further, nothing in Jacobsen *et al.*, 1996, discloses or suggests that doses in the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP, as recited in the instant claims, would be sufficient to inhibit alcohol dehydrogenase activity in humans *in vivo*, let alone would be effective in treating ethanol intolerance in subjects with reduced or absent ALDH2 activity.

Moreover, since Jacobsen *et al.*, 1996, discloses that a presumed therapeutic dose range of 10 to 20 mg/kg 4-MP is effective without the undesirable side effects of larger doses of 4-MP,[3] Applicants submit that Jacobsen *et al.*, 1996, provides no reason to further lower the dose range to 0.1 to 1.0 mg/kg 4-MP. Given the intended purpose for administering 4-MP disclosed in Jacobsen *et al.*, 1996, *i.e.*, treatment of methanol and ethylene glycol poisonings, one skilled in the art would have no reason to lower the dose of 4-MP below the presumed therapeutic dose range.

The '620 application, Casavant, and Jacobson *et al.*, 1996, either alone or in combination, do not teach or suggest doses within the range of about 0.1 mg/kg to about 1.0 mg/kg 4-MP to treat subjects with reduced or absent ALDH2 activity, as recited in claims 1-12, 21 and 22. Consequently, claims 1-12, 21 and 22 are not obvious over the '620 application in view of Casavant and Jacobson *et al.*, 1996.

Accordingly, Applicants respectfully request that the rejection of claims 1-12, 21 and 22 under 35 U.S.C. § 103(a) as allegedly obvious over Japanese Unexamined Patent Application S57-106620(5) ("the '620 application") in view of Casavant, *Pediatrics*, Vol.

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[2] Jacobsen *et al.*, 1988, refers to the doses of Groups 1 and 2 as the "two lower doses." *See* Jacobsen *et al.*, 1988, page 519, column 2, paragraph 4.

[3] *See* Jacobsen *et al.*, 1996, page 804, second column, lines 13-14 ("doses of 4-MP in the range of 10 to 20 mg/kg produce no adverse effects"). *See also* Jacobsen *et al.*, 1988, page 517, column 2, under Results ("[i]n Groups I (10 mg/kg) and 2 (20 mg/kg) there were no subjective or objective side-effects reported").

107, No. 1, January 2001, pp. 170 ("Casavant") and Jacobsen *et al.*, *Alcoholism: Clinical and Experimental Research*, Vol. 20, pp. 804-809 ("Jacobsen *et al.*, 1996") should be withdrawn.

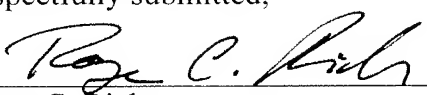
CONCLUSION

Applicants believe that the claims of the instant amendment meet all of the conditions for patentability and are in condition for allowance. Accordingly, an early indication of the same is respectfully requested.

No fee other than the fee for extension of time is believed to be due in connection herewith. However, should the Commissioner determine otherwise, the Commissioner is hereby authorized to charge any required fee(s) to Jones Day Deposit Account No. 50-3013 (order no. 451265-999001).

Respectfully submitted,

Date: February 24, 2010



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